

EXHIBIT C

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View of NCT01494805 on 2011_12_16

ClinicalTrials Identifier: NCT01494805

Updated: 2011_12_16

Descriptive Information

| | |
|-----------------------|---|
| Brief title | Safety and Efficacy Study of rAAV.sFlt-1 in Patients With Exudative Age-Related Macular Degeneration |
| Official title | A Phase I/II Controlled Dose-escalating Trial to Establish the Baseline Safety and Efficacy of a Single Subretinal Injection of rAAV.sFlt-1 Into Eyes of Patients With Exudative Age-related Macular Degeneration (AMD) |

Brief summary

The study will involve 24 patients aged 65 or above who have exudative age-related macular degeneration (wet AMD). Patients will be randomized to receive one of two doses of rAAV.sFlt-1 (16 patients) or assigned to the control group (8 patients). Patients in all three groups are eligible for rescue therapy with ranibizumab.

Detailed description

A new treatment for exudative age-related macular degeneration (wet AMD) is being investigated. The purpose of this Phase I/II clinical research study is to examine the baseline safety and efficacy of an experimental study drug to treat a complication of the disease which leads to vision loss. The name of the study drug is rAAV.sFlt-1.

This experimental study uses a non-pathogenic virus to express a therapeutic protein within the eye. The therapeutic is a naturally-occurring protein intended to diminish the growth of abnormal blood vessels under the retina. The duration of effect is thought to be long-term (years) following a single administration. The therapeutic is delivered to a small area underneath the retina (subretinal) in a short surgical procedure.

The clinical research study will look at the baseline safety and efficacy of a single injection of rAAV.sFlt-1 injected directly into the eye. There are 3 steps to this study. In the first step, patients will receive either low dose rAAV.sFlt-1 or control treatment. In the second step, patients will receive either the high dose rAAV.sFlt-1 or control treatment. In the third step patients will receive either the low dose rAAV.sFlt-1, the high dose rAAV.sFlt-1, or control treatment. Patients in all groups will be eligible for rescue therapy with ranibizumab throughout the study.

Twenty-four (24) patients will participate at 1 center in Australia. The primary

endpoint of the study is at one month, with extended follow up for 3 years.

| | |
|--------------------------|--|
| Phase | Phase 1 |
| Phase | Phase 2 |
| Study type | Interventional |
| Study design | Treatment |
| Study design | Randomized |
| Study design | Single Blind (Outcomes Assessor) |
| Study design | Parallel Assignment |
| Study design | Safety/Efficacy Study |
| Primary outcome | <p>Measure: No sign of unresolved ophthalmic complications, toxicity or systemic complications as measured by laboratory tests from 1 month post injection</p> <p>Time Frame: Primary endpoint at 1 month</p> <p>Safety Issue? Yes</p> <p>Description:</p> <ul style="list-style-type: none"> 1) Ocular examination: <ul style="list-style-type: none"> - Ocular inflammation - Intraocular pressure - Visual acuity - Retinal bleeding 2) Abnormal laboratory data |
| Secondary outcome | <p>Measure: Maintenance or improvement of vision without the necessity of ranibizumab re-injections</p> <p>Time Frame: Up to 3 years</p> <p>Safety Issue? No</p> <p>Description:</p> <ul style="list-style-type: none"> 1) Best-corrected visual acuity 2) CNV lesion 3) Foveal thickness |
| Enrollment | 24 (Anticipated) |
| Condition | Macular Degeneration |
| Condition | Age-related Maculopathies |
| Condition | Age-related Maculopathy |
| Condition | Maculopathies,Age-related |
| Condition | Maculopathy,Age-related |
| Condition | Retinal Degeneration |
| Condition | Retinal Neovascularization |
| Condition | Eye Diseases |
| Arm/Group | Arm Label: Low Dose rAAV.sFlt-1 Experimental |
| Arm/Group | Arm Label: High Dose rAAV.sFlt-1 Experimental |

| | | |
|---------------------|--|---------------------------------------|
| Arm/Group | Arm Label: Control - ranibizumab only | Active Comparator |
| Intervention | Biological/Vaccine: rAAV.sFlt-1 1 x 10^10 vector genomes (vg) rAAV.sFlt-1, delivered by subretinal injection | Arm Label: Low Dose rAAV.sFlt-1 |
| Intervention | Biological/Vaccine: rAAV.sFlt-1 1 x 10^11 vector genomes (vg) rAAV.sFlt-1, delivered by subretinal injection | Arm Label: High Dose rAAV.sFlt-1 |
| Intervention | Other: Control (ranibizumab alone) Patients will not receive rAAV.sFlt-1, but will be eligible for retreatment with ranibizumab (Lucentis). | Arm Label: Control - ranibizumab only |

Recruitment Information

| | |
|--------------------------------|-----------------------|
| Status | Recruiting |
| Start date | 2011-12 |
| Last follow-up date | 2014-12 (Anticipated) |
| Primary completion date | 2012-12 (Anticipated) |
| Criteria | |

Inclusion Criteria:

- Age greater than or equal to 65 years;
- Subfoveal CNV secondary to AMD and with best corrected visual acuity of 3/60 - 6/24 with 6/60 or better in the other eye;
- Fluorescein angiogram of the study eye must show evidence of a leaking subfoveal choroidal neovascular lesion;
- Must be a candidate for anti-VEGF intravitreal injections;
- The entire dimension of the lesion must not exceed 12 Macular Photocoagulation Study disc areas;
- No previous retinal treatment of photodynamic therapy or laser;
- Able to provide informed consent;
- Participant has clinically acceptable laboratory and ECG at the time of enrolment; and
- Able to comply with protocol requirements, including follow-up visits.

Exclusion Criteria:

- Liver enzymes > 2 X upper limit of normal;
- Clinical evidence of active infection of any type, including adenovirus, hepatitis A, B, or C, or HIV virus;
- Any prior treatment for AMD in the study / control eye, excluding anti-VEGF injections;
- A tear in the retinal pigmented epithelium;

- Extensive submacular scar tissue;
- Significant retinal disease other than subfoveal CNV AMD, such as diabetic retinopathy or retinal vascular occlusion;
- Significant non-retinal disease such as ocular atrophy or cataracts;
- Known allergy to fluorescein;
- Current use of prednisolone, other anti-inflammatory steroids or immune suppression drugs. Non-steroidal drugs such as aspirin are allowed;
- Any other significant disease or disorder which, in the opinion of the Investigator, may either put the participants at risk because of participation in the study, or may influence the result of the study, or the participant's ability to participate in the study;
- Participants who have participated in another research study involving an investigational product in the past 12 weeks; and
- Penicillin sensitivity.

Gender Both
Minimum age 65 Years
Healthy volunteers No

Administrative Data

Organization name Lions Eye Institute, Perth, Western Australia
Organization study ID 2008-135
Sponsor Lions Eye Institute, Perth, Western Australia
Collaborator Avalanche Biotechnologies, Inc.
Health Authority Australia: Department of Health and Ageing Therapeutic Goods Administration

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Changes to NCT01494805 on 2012_09_11

Type of info changed: Protocol, Recruitment, Administrative, Misc.

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| 2 | | | NCT01494805 |
| 3 | </nct_id> <textblock> | </nct_id> <textblock> | |
| 4 | The study will involve 24 patients aged 65 or above who have exudative age-related macular degeneration (wet AMD). Patients will be randomized to receive one of two doses of rAAV.sFlt-1 (46 patients) or assigned to the control group (8 patients) . Patients in all three groups are eligible for rescue therapy with ranibizumab. | | The study will involve 48 patients aged 55 or above who have exudative age-related macular degeneration (wet AMD). Patients will be randomized to receive one of two doses of rAAV.sFlt-1 or assigned to the control group . |
| 5 | </textblock> | </textblock> | |
| 6 | This experimental study uses a non-pathogenic virus to express a therapeutic protein within the eye. The therapeutic is a naturally-occurring protein intended to diminish the growth of abnormal blood vessels under the retina. The duration of effect is thought to be long-term (years) following a single administration. The therapeutic is delivered to a small area underneath the retina (subretinal) in a short surgical procedure. | | This experimental study uses a non-pathogenic virus to express a therapeutic protein within the eye. The therapeutic diminishes the growth of abnormal blood vessels under the retina. The duration of effect is thought to be long-term (years) following a single administration. |
| 7 | | | |
| 8 | The clinical research study will look at the baseline safety and efficacy of a single injection of rAAV.sFlt-1 injected directly into the eye. There are 3 steps to this study: In the first step, patients will receive either low dose rAAV.sFlt-1 or control treatment. In the second step, patients will receive either the high dose rAAV.sFlt-1 or control treatment. In the third step patients will receive either the low dose | The clinical research study will look at the baseline safety and efficacy of a single injection of rAAV.sFlt-1 injected directly into the eye. | |

Key

| | | |
|----|--|--|
| | <p style="color: red;">rAAV-sFlt-1, the high dose rAAV-sFlt-1, or control treatment. Patients in all groups will be eligible for rescue therapy with ranibizumab throughout the study.</p> | |
| 9 | | |
| 10 | <p>Twenty-four (24) patients will participate at 4 center in Australia. The primary endpoint of the study is at one month, with extended follow up for 3 years.</p> | <p>Forty-eight (48) patients will participate in Australia. The primary endpoint of the study is at one month, with extended follow up for 3 years.</p> |
| 11 | </textblock> | </textblock> |
| 12 | <date> 2011-12 | <date> 2012-09 |
| 13 | </date> | </date> |
| 14 | <date> 2012-12 | <date> 2013-06 |
| 15 | </date> | </date> |
| 16 | > 24 | > 48 |
| 17 | </enrollment> | </enrollment> |
| 18 | <p>Inclusion Criteria:</p> <p>&#8226; Age greater than or equal to 65 years; &#8226; Subfoveal CNV secondary to AMD and with best corrected visual acuity of 3/60 - 6/24 with 6/60 or better in the other eye; &#8226; Fluorescein angiogram of the study eye must show evidence of a leaking subfoveal choroidal neovascular lesion;</p> | <p>Inclusion Criteria:</p> <p>&#8226; Age greater than or equal to 55 years; &#8226; Subfoveal CNV secondary to AMD and with best corrected visual acuity of 3/60 - 6/9 with 6/60 or better in the other eye; &#8226; Fluorescein angiogram of the study eye must show evidence of a leaking subfoveal choroidal neovascular lesion, or CNV currently under active management with anti-VEGF therapy;</p> |
| 19 | • Must be a candidate for anti-VEGF intravitreal injections; | • Must be a candidate for anti-VEGF intravitreal injections; |
| 20 | • The entire dimension of the lesion must not exceed 12 Macular Photocoagulation Study disc areas; | |
| 21 | • No previous retinal treatment of photodynamic therapy or laser; • Able to provide informed consent; | • No previous retinal treatment of photodynamic therapy or laser; • Able to provide informed consent; |
| 22 | • Participant has clinically acceptable laboratory and ECG at the time of enrolment; and | |
| 23 | • Able to comply with protocol requirements, including follow-up visits. • Liver enzymes > 2 X upper limit of normal; | • Able to comply with protocol requirements, including follow-up visits. • Liver enzymes > 2 X upper limit of normal; |
| 24 | • Clinical evidence of active | |

| | | |
|----|--|--|
| | infection of any type, including adenovirus, hepatitis A, B, or C, or HIV virus; | |
| 25 | • Any prior treatment for AMD in the study / control eye, excluding anti-VEGF injections; | • Any prior treatment for AMD in the study / control eye, excluding anti-VEGF injections; |
| 26 | • A tear in the retinal pigmented epithelium; • Extensive submacular scar tissue; • Significant retinal disease other than subfoveal CNV AMD, such as diabetic retinopathy or retinal vascular occlusion; • Significant non-retinal disease such as ocular atrophy or cataracts; • Known allergy to fluorescein; • Current use of prednisolone, other anti-inflammatory steroids or immune suppression drugs. Non-steroidal drugs such as aspirin are allowed; • Any other significant disease or disorder which, in the opinion of the Investigator, may either put the participants at risk because of participation in the study, or may influence the result of the study, or the participant's ability to participate in the study; • Participants who have participated in another research study involving an investigational product in the past 12 weeks; and • Penicillin sensitivity. | |
| 27 | | • Extensive sub-foveal scarring, extensive geographic atrophy, or thick subretinal blood in the study eye as determined by the investigator; • Significant retinal disease other than sub-foveal CNV AMD; |
| 28 | + </textblock> <minimum_age> 65 Years | + </textblock> <minimum_age> 55 Years |
| 29 | | |
| 30 | + </minimum_age> <last_release_date> | + </minimum_age> <last_release_date> |
| 31 | 2011-12-15 | 2012-09-11 |
| 32 | + </last_release_date> </clinical_study> | + </last_release_date> </clinical_study> |

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Changes to NCT01494805 on 2013_12_19

Type of info changed: Misc.

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| 2 | | |
| 3 | | |
| 4 | | <is_section_801> No </is_section_801> |
| 5 | +<brief_title> <date> 2014-12 </date> | +<brief_title> <date> 2016-12 </date> |
| 6 | | |
| 7 | </date> | </date> |
| 8 | | |
| 9 | <date> 2013-06 </date> | <date> 2014-06 </date> |
| 10 | | |
| 11 | <last_release_date> 2012-09-11 </last_release_date> | <last_release_date> 2013-12-18 </last_release_date> |
| | | |
| | </clinical_study> | </clinical_study> |

| Key | |
|--------|-------------------------------------|
| Before | After |
| 1 | Unchanged. |
| 2 | Deleted. |
| 3 | Changed from this... ...to this. |
| 4 | Added. |
| *** | *** |

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Changes to NCT01494805 on 2014_02_25

Type of info changed: Protocol, Misc.

| | Before <i>(Updated 2013_12_19)</i> | After <i>(Updated 2014_02_25)</i> |
|----|---|--|
| 1 | <clinical_study> | <clinical_study> |
| 2 | <p>Forty-eight (48) patients will participate in Australia. The primary endpoint of the study is at one month, with extended follow up for 3 years.</p> | <p>A minimum of thirty-nine (39) and up to forty-eight (48) subjects will participate in Australia. The primary endpoint of the study is at one month, with extended follow up for 3 years.</p> |
| 3 | </textblock> | </textblock> |
| 4 | <date> 2016-12 | <date> 2017-04 |
| 5 | </date> | </date> |
| 6 | <date> 2014-06 | <date> 2015-04 |
| 7 | </date> | </date> |
| 8 | <keyword> | AAV </keyword> |
| 9 | AMD <last_release_date> | AMD <last_release_date> |
| 10 | 2013-12-18 | 2014-02-24 |
| 11 | </last_release_date> | </last_release_date> |
| | </clinical_study> | </clinical_study> |

| Key | |
|--------|----------------------|
| Before | After |
| 1 | Unchanged. |
| 2 | Deleted. |
| 3 | Changed from this... |
| 4 | Added. |
| *** | *** |

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Changes to NCT01494805 on 2014_03_18

Type of info changed: Protocol, Misc.

| | Before (Updated 2014_02_25) | After (Updated 2014_03_18) |
|----|--|--|
| 1 | <clinical_study> <textblock> | <clinical_study> <textblock> |
| 2 | The study will involve 48 patients aged 55 or above who have exudative age-related macular degeneration (wet AMD). Patients will be randomized to receive one of two doses of rAAV.sFlt-1 or assigned to the control group. | The study will involve approximately 40 subjects aged 55 or above who have exudative age-related macular degeneration (wet AMD). Patients will be randomized to receive one of two doses of rAAV.sFlt-1 or assigned to the control group. |
| 3 | </textblock> | </textblock> |
| 4 | A minimum of thirty-nine (39) and up to forty-eight (48) subjects will participate in Australia. The primary endpoint of the study is at one month, with extended follow up for 3 years. | Approximately forty (40) subjects will participate in Australia. The primary endpoint of the study is at one month, with extended follow up for 3 years. |
| 5 | </textblock> <date> | </textblock> <date> |
| 6 | 2017-04 | 2017-05 |
| 7 | </date> | </date> |
| 8 | <date> 2015-04 | <date> 2015-05 |
| 9 | </date> | </date> |
| 10 | > 48 | > 40 |
| 11 | </enrollment> | </enrollment> |
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| 13 | </last_release_date> <clinical_study> | </last_release_date> <clinical_study> |

Key


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Changes to NCT01494805 on 2014_04_09

Type of info changed: Recruitment status, Misc.

| Before (Updated 2014_03_18) | | After (Updated 2014_04_09) |
|---------------------------------------|----------------------|--------------------------------------|
| 1 | <clinical_study> | <clinical_study> |
| | <status> | <status> |
| 2 | Recruiting | Active, not recruiting |
| 3 | </status> | </status> |
| | <last_release_date> | <last_release_date> |
| 4 | 2014-03-17 | 2014-04-09 |
| 5 | </last_release_date> | </last_release_date> |
| | </clinical_study> | </clinical_study> |

| | |
|-----|--|
| Key | |
|-----|--|

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View of NCT01494805 on 2014_04_09

ClinicalTrials Identifier: NCT01494805

Updated: 2014_04_09

Descriptive Information

Brief title Safety and Efficacy Study of rAAV.sFlt-1 in Patients With Exudative Age-Related Macular Degeneration

Official title A Phase I/II Controlled Dose-escalating Trial to Establish the Baseline Safety and Efficacy of a Single Subretinal Injection of rAAV.sFlt-1 Into Eyes of Patients With Exudative Age-related Macular Degeneration (AMD)

Brief summary

The study will involve approximately 40 subjects aged 55 or above who have exudative age-related macular degeneration (wet AMD). Patients will be randomized to receive one of two doses of rAAV.sFlt-1 or assigned to the control group.

Detailed description

A new treatment for exudative age-related macular degeneration (wet AMD) is being investigated. The purpose of this Phase I/II clinical research study is to examine the baseline safety and efficacy of an experimental study drug to treat a complication of the disease which leads to vision loss. The name of the study drug is rAAV.sFlt-1.

This experimental study uses a non-pathogenic virus to express a therapeutic protein within the eye. The therapeutic diminishes the growth of abnormal blood vessels under the retina. The duration of effect is thought to be long-term (years) following a single administration.

The clinical research study will look at the baseline safety and efficacy of a single injection of rAAV.sFlt-1 injected directly into the eye.

Approximately forty (40) subjects will participate in Australia. The primary endpoint of the study is at one month, with extended follow up for 3 years.

Phase Phase 1

Phase Phase 2

Study type Interventional

Study design Treatment

Study design Randomized

Study design Single Blind (Outcomes Assessor)

| | |
|--------------------------|--|
| Study design | Parallel Assignment |
| Study design | Safety/Efficacy Study |
| Primary outcome | <p>Measure: No sign of unresolved ophthalmic complications, toxicity or systemic complications as measured by laboratory tests from 1 month post injection</p> <p>Time Frame: Primary endpoint at 1 month</p> <p>Safety Issue? Yes</p> <p>Description:</p> <ul style="list-style-type: none"> 1) Ocular examination: <ul style="list-style-type: none"> - Ocular inflammation - Intraocular pressure - Visual acuity - Retinal bleeding 2) Abnormal laboratory data |
| Secondary outcome | <p>Measure: Maintenance or improvement of vision without the necessity of ranibizumab re-injections</p> <p>Time Frame: Up to 3 years</p> <p>Safety Issue? No</p> <p>Description:</p> <ul style="list-style-type: none"> 1) Best-corrected visual acuity 2) CNV lesion 3) Foveal thickness |
| Enrollment | 40 (Anticipated) |
| Condition | Macular Degeneration |
| Condition | Age-related Maculopathies |
| Condition | Age-related Maculopathy |
| Condition | Maculopathies,Age-related |
| Condition | Maculopathy,Age-related |
| Condition | Retinal Degeneration |
| Condition | Retinal Neovascularization |
| Condition | Eye Diseases |
| Arm/Group | Arm Label: Low Dose rAAV.sFlt-1 Experimental |
| Arm/Group | Arm Label: High Dose rAAV.sFlt-1 Experimental |
| Arm/Group | Arm Label: Control - ranibizumab only Active Comparator |
| Intervention | Biological/Vaccine: rAAV.sFlt-1 Arm Label: Low Dose rAAV.sFlt-1 |
| | 1 x 10^10 vector genomes (vg) rAAV.sFlt-1, delivered by subretinal injection |
| Intervention | Biological/Vaccine: rAAV.sFlt-1 Arm Label: High Dose rAAV.sFlt-1 |

1 x 10¹¹ vector genomes (vg) rAAV.sFlt-1, delivered by subretinal injection

| | | |
|--|------------------------------------|---------------------------------------|
| Intervention | Other: Control (ranibizumab alone) | Arm Label: Control - ranibizumab only |
| Patients will not receive rAAV.sFlt-1, but will be eligible for retreatment with ranibizumab (Lucentis). | | |

Recruitment Information

| | |
|--------------------------------|------------------------|
| Status | Active, not recruiting |
| Start date | 2011-12 |
| Last follow-up date | 2017-05 (Anticipated) |
| Primary completion date | 2015-05 (Anticipated) |

Criteria

Inclusion Criteria:

- Age greater than or equal to 55 years;
- Subfoveal CNV secondary to AMD and with best corrected visual acuity of 3/60 - 6/9 with 6/60 or better in the other eye;
- Fluorescein angiogram of the study eye must show evidence of a leaking subfoveal choroidal neovascular lesion, or CNV currently under active management with anti-VEGF therapy;
- Must be a candidate for anti-VEGF intravitreal injections;
- No previous retinal treatment of photodynamic therapy or laser;
- Able to provide informed consent;
- Able to comply with protocol requirements, including follow-up visits.

Exclusion Criteria:

- Liver enzymes > 2 X upper limit of normal;
- Any prior treatment for AMD in the study / control eye, excluding anti-VEGF injections;
- Extensive sub-foveal scarring, extensive geographic atrophy, or thick subretinal blood in the study eye as determined by the investigator;
- Significant retinal disease other than sub-foveal CNV AMD;

| | |
|---------------------------|----------|
| Gender | Both |
| Minimum age | 55 Years |
| Healthy volunteers | No |

Administrative Data

| | |
|------------------------------|--|
| Organization name | Lions Eye Institute, Perth, Western Australia |
| Organization study ID | 2008-135 |
| Sponsor | Lions Eye Institute, Perth, Western Australia |
| Collaborator | Avalanche Biotechnologies, Inc. |
| Health Authority | Australia: Department of Health and Ageing Therapeutic |

Goods Administration